Does cancer risk affect health-related quality of life in patients with Barrett’s esophagus?

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Background: Health-related quality of life is decreased in patients with GERD and Barrett’s esophagus (BE).

Objective: To determine whether time-tradeoff (TTO) values would differ in patients with BE when patients were asked to trade away the potential risk of esophageal adenocarcinoma rather than chronic heartburn symptoms.

Design: A prospective clinical trial.

Patients: Subjects with biopsy-proven BE.

Interventions: Custom-designed computer program to elicit health-state utility values, quality of life in reflux and dyspepsia (QOLRAD), and Medical Outcomes Survey short form-36 surveys.

Main Outcome Measurements: TTO utility values for the annual cancer-risk–associated current health state and for hypothetical scenarios of dysplasia and esophageal cancer.

Results: We studied 60 patients in the cancer-risk cohort (57 men, 92% veteran; mean age [standard deviation; SD], 65 years [11 years], mean GERD duration 17 years [12 years]). The heartburn cohort included 40 patients with GERD and BE with TTO values derived for GERD symptoms. The mean (SD) utility for nondysplastic BE was 0.91 (0.15) compared with 0.90 (0.12) for the heartburn cohort (P = .7). The mean utility values were significantly lower for scenarios of low-grade dysplasia (0.85 [0.12], P = .02) and high-grade dysplasia (0.77 [0.14], P < .005). The mean TTO was 0.67 (0.19) for the scenario of esophageal cancer. There was no correlation between the utility scores and the disease-specific survey scores.

Limitations: TTO values were hypothetical for states of dysplasia and cancer.

Conclusions: TTO utility values based on heartburn symptoms or annual risk of cancer in patients with non-dysplastic BE are roughly equivalent. However, TTO utility values are significantly lower for health states with increasing cancer risks. (Gastrointest Endosc 2007;65:16-25.)

Patients with chronic reflux symptoms are at risk for the development of Barrett’s esophagus (BE), a metaplastic change of the normal squamous mucosa to a specialized intestinal epithelium and subsequent progression to adenocarcinoma of the esophagus. Approximately 10% to 15% of the patients with chronic GERD will have BE detected during endoscopic examination, although this number may be as high as 20% in the general population. Patients with BE harbor a risk of cancer of approximately 0.5% per year, with increasing neoplastic risk in patients who develop dysplasia.

Most patients with BE have from chronic symptoms of gastroesophageal reflux and require daily medical therapy for adequate symptom control. Multiple studies have demonstrated that chronic heartburn symptoms adversely affect health-related quality of life. Administration of the Medical Outcomes Survey Short Form 36 (SF-36) to patients with chronic reflux has shown that patients with untreated heartburn symptoms score lower than U.S. population normal controls on all 8 subscales of the SF-36 and that these scores return to normal with medical therapy that adequately controls reflux symptoms. Health-state utilities are preference-weighted measures required for cost-effectiveness analyses. Utility measurements are designed to provide a numerical indicator of symptom severity based on a scale of 0 to 1.0, where
0 represents death or a state equivalent to death, and 1.0 represents ideal health, or a state without a particular disease, eg, heartburn. By using a custom-designed computer program to elicit utility values, we recently demonstrated that time-tradeoff (TTO) values in patients with heartburn when off antireflux therapy approached the values for other chronic medical conditions, such as angina pectoris, congestive heart failure, and asthma. In this prior quality-of-life study, the TTO values did not vary significantly according to the presence or the absence of BE. The patients with BE in the study had both endoscopic and histologic confirmation of the diagnosis, and had been educated about the associated risk of esophageal cancer before the initial TTO interview.

Current guidelines recommend endoscopic surveillance for patients with nondysplastic BE every 3 years. These guidelines are based on indirect evidence that suggests that endoscopic screening and surveillance may detect cancers at an earlier and more curable stage. The small underlying risk of cancer in patients with BE may adversely affect health-related quality of life. The purpose of this prospective study was to determine whether TTO values would differ in patients with BE when patients were asked to trade away the potential risk of esophageal adenocarcinoma rather than chronic heartburn symptoms.

PATIENTS AND METHODS

The study was conducted at Stanford University Hospital and the Veteran’s Administration (VA) Palo Alto Health Care System. Patients who were identified to have BE between 1998 and 2003 were sent a letter of invitation that explained the purpose of the study. Interested patients were instructed to contact one of the investigators or to return the letter and indicate permission to be contacted. Potential subjects were interviewed by one of the investigators either before upper endoscopy for BE surveillance or during an arranged interview with one of the investigators. We also recruited patients who were scheduled for endoscopic surveillance of BE at either Stanford University Hospital or the VA Palo Alto Health Care System by sending a letter of invitation followed by a telephone call to arrange for the interview before endoscopy if the subjects were interested in participation. Reports from prior endoscopic examinations and pathology reports were reviewed to confirm the presence of intestinal metaplasia in tongues of salmon-colored mucosa that extended at least 0.5 mm from the esophagogastric junction. We included patients with BE with either no dysplasia, low-grade dysplasia (LGD), or high-grade dysplasia (HGD), but not patients with esophageal cancer. Exclusion criteria also included the presence of a terminal illness, eg, unresectable cancer; an inability to interact with the computer program; or an inability to provide informed consent.

All interviews were conducted either by Dr Gerson or the study coordinator (Dr Ullah). The study coordinator was trained by using a previously used instruction protocol developed for a prior quality-of-life study funded by NIH/NIA R01 AG15110. Patients included in the heartburn group of the study had been previously interviewed by using a custom-designed program to elicit health-state utility values for heartburn symptoms. The study was conducted under the approval from the Human Subject Panel for Stanford University and the VA Palo Alto Health Care System.

Utility and questionnaire assessment

A computer program for assessing utilities was used to facilitate standardization of the interview. The program, Utility Assessor, was developed by the investigators in accordance with standard utility methods. After entry of the age of the patient into the first screen, the program calculated life expectancy based upon the 2002 United States Life Tables for use in the subsequent TTO utility questions. Patients were instructed to identify any chronic condition that required medical therapy of at least 6 months’ duration by checking boxes that listed various medical conditions on the first screen. These potential conditions included asthma; cardiovascular disease; hypertension; lung disease; allergic rhinitis; congenital heart lesions; diabetes; stroke; arthritis; chronic liver or renal disease; psychiatric disease, including bipolar disorder; anxiety; and/or depression; glaucoma; infectious or sexually transmitted disease; HIV infection; or “other” category. Any patient with a chronic medical or psychologic condition that required more than 6 months of medical therapy was considered to have a comorbid condition.

Capsule Summary

What is already known on this topic

- Health-related quality of life is decreased in patients with GERD and BE but can be improved with medical therapy that adequately controls symptoms.
- Patients with BE without dysplasia have a yearly cancer risk of approximately 0.5%, and this risk increases in patients who develop dysplasia.

What this study adds to our knowledge

- In a single-center, prospective, cohort study, TTO utility values based on heartburn symptoms or the annual risk of cancer were roughly equivalent in patients with nondysplastic BE. However, values for hypothetical states of dysplasia (cancer risk of 2.5% or greater) were significantly lower.
- The duration of antisecretory therapy was an important predictor of the TTO score, and younger patients were more likely to have a higher TTO score for the cancer scenario.
Patients initially provided assessments for their current health state, including all of their active medical problems. By using a visual analog rating system, patients were shown a scale where 0 was the worst possible health state or death, and 100 represented a state of perfect health, without heartburn or any other health problems. The cursor started in the middle of the bar at 50 and was displaced by the research assistant according to the patient’s instructions until the patient arrived at a decision about the current value of his or her health.

To train patients how to respond to the utility questions, we next administered a practice question by using the TTO technique with a hypothetical scenario of vision loss. The subject was instructed to imagine a state of blindness with 10 remaining years to live and was asked how much of his life he would be willing to trade to restore perfect vision. The calculated utility value was displayed to the patient after the practice question. The TTO value was equivalent to 1 minus the number of years traded divided by the number of life-years remaining. The utility value for the practice question was not recorded, because the purpose of the question was to provide the patient with an opportunity to practice the concept of TTO. Patients who did not understand the practice question could receive further training by the research assistant, who would not advance to the actual utility scenarios until comprehension was obtained. All patients in our current study were able to understand the task and to proceed to the actual rating.

We subsequently educated patients about the concept of an annual risk of death by using risk estimates obtained from the Harvard Risk Analysis Web site for events, including motor vehicle accident (annual risk of 1/6745 events), fire (1/82,977), lightening (1/4,478,159), stroke (1/699), and heart disease (1/397). On the same screen, we educated patients that the annual risk of esophageal cancer and subsequent death in patients with BE was 1 per 250. Patients were advised to contact Dr. Gerson if they experienced emotional distress as a result of the questions in the computer program. None of the 60 enrolled patients in the study reported emotional distress during the interviews.

We then counseled patients about the current surveillance guidelines for patients with nondysplastic BE. Upper endoscopic examinations for cancer surveillance were recommended every 3 years and were associated with a risk of hemorrhage and/or perforation at a rate of 1 per 10,000 examinations. Patients were asked to imagine that they could either spend their remaining life-years with BE, described as a health state that would include an ongoing need for endoscopic surveillance and a 0.5% annual risk of esophageal cancer or they could trade away the BE by reducing their remaining life-years an amount of time that they would determine.

On the subsequent screen that presented the first TTO scenario for nondysplastic BE, subjects were presented with the average number of remaining life-years calculated from the current 2002 U.S. Life Tables according to the age and sex entered into the program. Patients were then asked how many years or months they were willing to trade in exchange for nondysplastic BE. Patients were allowed to trade no time, as little as 1 month, or up to the maximum number of remaining life-years. The computer program used a recursive “ping-pong” algorithm to arrive at an unbiased answer. During the experiment, the research associate was instructed not to offer comments that would bias the subjects in terms of their answers. However, patients who chose not to trade away any of their life were questioned by the assistant to ensure comprehension of the question.

The initial TTO screen asked patients to trade away their BE plus any other comorbid conditions. The subsequent TTO screen asked subjects to trade away all of the other medical conditions other than BE that were identified by the patient at the start of the program. This TTO scenario for other comorbid conditions was not repeated for any of the other BE scenarios, but the value obtained from this screen was used to calculate subsequent TTO values for hypothetical scenarios of dysplasia and cancer.

We subtracted any decrement in quality of life because of other comorbid conditions to derive the decrement in health-related quality of life attributable only to the cancer risk associated with the BE. For example, a 55-year-old man with BE, asthma, and hypertension would be asked how much of 24 years he would trade to be restored to perfect health. If the patient elected to trade 10 years of his life to exchange his BE and other problems for perfect health, and then 5 years to trade the asthma and hypertension, his TTO utility would be \[1 - (10 + 5)/24\] or 0.79. Patients who did not have any comorbid conditions or who would not trade any of their life would have a utility of 1.0 or a utility equivalent to perfect health. A subject with a serious comorbid condition, such as end-stage renal disease, might attribute very little weight to the risk of esophageal cancer associated with BE and might trade the same amount of time for the renal disease alone and the cancer risk plus the renal disease, which would also result in a score of 1.0.

After the initial TTO question for nondysplastic BE, the computer program then described a hypothetical scenario of BE with LGD that would be associated with an annual cancer risk of 2.5% per year. Patients were advised to undergo surveillance endoscopy on a yearly basis and again were asked how much of their remaining life years they would trade for the hypothetical scenario of BE with LGD.

Patients were next instructed to imagine a scenario of HGD where the annual cancer risk would be 5% per year, and surveillance endoscopy would be recommended every 3 months. Patients were not offered any endoscopic or surgical therapy for HGD, because the goal of...
the study was to derive the decrement in health-related quality of life because of the cancer risk associated with HGD.

Although we did not enroll patients diagnosed with esophageal cancer, the purpose of the study was to describe potential cancer risks associated with BE, including the hypothetical scenario of esophageal-cancer development. Because the 5-year survival rates in patients with esophageal cancer are known to approximate 80% for patients in an endoscopic surveillance program and 20% for patients without prior diagnosis or surveillance of BE, we chose a fixed life expectancy of 5 years for the cancer TTO question. Patients were instructed that if they were deemed operative candidates, then they would be offered an esophagectomy that would cure the cancer but would be associated with significant morbidity and mortality, including a perioperative mortality rate of 5%; a 2-week hospital stay, with a possible intensive care unit stay of 2 to 5 days; and symptoms of dysphagia, early satiety, and postprandial diarrhea that would likely improve over time. In patients who were theoretically diagnosed with metastatic disease, there would be a transition from local to metastatic cancer, and chemotherapy, radiation therapy, and esophageal stent placement would be offered as palliative therapy. Symptoms associated with esophageal cancer and palliative therapy, including dysphagia, nausea, vomiting, oral ulcerations, diarrhea, and weakness, were described to the patient. We did not provide endoscopic therapy as a treatment option for patients who were not surgical candidates, because the primary aim of the study was to derive the decrement in health-related quality of life because of esophageal adenocarcinoma. We, therefore, educated patients about treatments associated with both resectable and unresectable cancer but only derived a TTO value for the hypothetical state of esophageal cancer. On the final screen, patients were questioned about their annual household income level and their personal level of education.

All subjects completed the Quality of Life in Reflux and Dyspepsia (QOLRAD) survey; the Reflux Disease Questionnaire (RDQ), and the SF-36 while on antisecretory therapy. SF-36 data were scored by using transformed scores analyzed by SF Health Outcomes Scoring Software (QualityMetric Inc, Lincoln, RI). We obtained SF-36 scores to determine whether we could predict TTO values based on the SF-36 scores. We obtained data by using the QOLRAD and RDQ to determine whether there was a correlation between the disease-specific surveys and the utility values. Patients received $50 for completion of the interview and questionnaires.

Statistical analysis

The χ² tests were used to analyze categorical variables by using Hintze L. Number Cruncher Statistical Systems, 2001, (NCSS, Kaysville, Utah). Paired Student t tests were used in Microsoft Excel 2000 (Microsoft Corp, Redmond, Wash) to analyze continuous variables. The level of significance was set at P < .05. All tests were 2-tailed.

We used linear regression to analyze the relation between the TTO values and potential predictors. Mixed-effects linear regression was performed for TTO scores. Initial histograms indicated that these response data were peaked at 1.0 (perfect health) and skewed to the left of 1.0. Because the utility scores are numbers that are skewed and bounded between 0 and 1, we applied the ‘‘logit’’ transformation. The ‘‘started’’ logit transformation of the TTO scores made these distributions appear more Gaussian (although the peak on the right remains). We used started logits to deal with responses that were exactly 1.0 by using the formula log((p + c)/(1 − p + c)), where p is proportion, and c > 0 is a small constant (1/200).

The 7 potential predictor variables in the regression model included patient age, sex, ethnicity, site of care at VA medical center, duration of heartburn symptoms, years on medications, and the presence or the absence of comorbid conditions. We created scatterplots to determine a potential correlation between utility values and questionnaire scores. Because there was multiple testing of outcome data arising from individual patients, it is indicated wherever correction of P values by the Bonferroni method would remove statistical significance.

Sample-size calculations

We hypothesized that health-related quality of life would be lower when patients were asked to trade away their potential risk of esophageal adenocarcinoma rather than their chronic heartburn symptoms. The study was designed to detect a potential difference in utility values of at least 10% (change in utility of approximately 0.1) with a 2-tailed α of 0.05 and a power of 90% between the TTO uses for the health state of having BE provided as a rating of current symptoms and the TTO values for health states of BE according to an associated risk of cancer. To detect this difference, we calculated that we would require at least 30 patients in the heartburn group (patients with BE from the prior quality-of-life study with TTO values based on heartburn symptoms), and 30 patients in the cancer-risk group, with TTO scores based on cancer risk associated with BE.

RESULTS

A total of 130 patients were recruited for the study. Fifty-five patients with known BE from 1998 to 2003 were sent letters of invitation, and an additional 75 patients scheduled for endoscopic surveillance were invited to participate. Twenty patients (36%) from the 1998 to 2003 database agreed to participate, in addition to 40 patients (53%) who were scheduled for endoscopic
surveillance examinations. Therefore, the overall participation rate was 60 of 130 or 46%. The participation rate was 55 of 95 (58%) for the invited veteran subjects, and 5 of 35 (14%) for the nonveteran participants. Thirty-five patients (27%) refused to participate either in person at the time of surveillance endoscopy or by returning the letter of invitation, and the remaining 35 patients did not respond to the letter of invitation. Seven (12%) of the patients with BE had previously participated in our prior quality-of-life study that required patients be asked to trade away heartburn symptoms while both on and off of antisecretory therapy.10

Most (95%) of the patients were men (92% veteran), with a mean (SD) age of 65 years (11 years). Eighty percent (48/60) were white, 3 African American (5%), 6 Hispanic (10%), and 5 of Asian descent (5%). Twenty-seven patients (45%) had long-segment (>3 cm) BE and 57 (95%) had nondysplastic BE. At the time of the interview, 2 patients were classified as having LGD on the most recent endoscopic examination, and 1 patient had HGD.

BE was diagnosed within 1 year or less in 19 (32%) of patients (mean 0.65 years [0.5 years]; range, 2 months to 1 year) and over 1 year or more in the remaining 41 patients (mean, 5.2 years [2.5 years]; range, 2-11 years). All of the patients with BE were using proton pump inhibitor (PPI) therapy; thirty-two patients (53%) received therapy once daily, 25 (42%) twice daily, and 3 as needed. An additional 2 patients took H2-receptor antagonist therapy in addition to once-daily PPI therapy. Two thirds (40/60) of the patients had completed 12th grade or some college education, and 48% reported annual income levels between $15,000 and $65,000. All of the patients had comorbid conditions. Self-reported comorbid conditions included hypertension in 38 patients (63%), cardiac disease in 18 (30%), peptic ulcer disease in 17 (28%), pulmonary disease in 12 (20%), diabetes mellitus in 14 (23%), asthma in 21 (35%), sinus condition in 13 (22%), chronic cough in 13 (22%), arthritis in 35 (58%), anemia in 9 (15%), depression in 17 (28%), anxiety disorder in 11 (18%), prior cancer in 18 (30%), and chronic pain in 28 (47%). Of the 18 patients who had cancer, 7 had prostate cancer; 6 had skin cancer; and 1 patient each had prior meningioma, bladder cancer, neck cancer, oropharyngeal cancer; and 1 patient had a history of colon cancer 2 years before the interview. Other less common disorders included renal or liver disorders, stroke, glaucoma, sexually transmitted disease, and other psychologic disorders.

The demographic information for the 60 patients in the cancer-risk cohort compared with the 40 patients in the heartburn cohort (patients with BE who participated in the prior symptom-based TTO study) are shown in Table 1. Patients enrolled in the current study were significantly older (P = .02) compared with the patients in the heartburn group but were otherwise similar with regard to the percentage of male patients and number of years with reflux.

Results from the health-related quality-of-life interviews are shown in Table 2. We used the visual analog scale as a potential predictor for TTO scores. Visual analog scales were similar in patients in the current study compared with patients participating in the heartburn cohort (P = .23). The mean (SD) TTO value for nondysplastic BE was 0.91 (0.13) and did not differ significantly when compared with 0.90 (0.12) for the symptom-derived health-state utility values obtained while patients were on antireflux therapy (P = .7). When the data were reanalyzed after removing the 7 patients who had participated in the prior quality-of-life study 3 years ago or the 18 patients with prior personal history of cancer, there was no significant difference in TTO scores. In addition, the results did not change when the third of patients with less than a 12th grade education were excluded. There was no significant difference between the TTO values for

### TABLE 1. Baseline characteristics of the study population

<table>
<thead>
<tr>
<th>Parameter*</th>
<th>Cancer risk cohort, TTO values (N = 60)</th>
<th>Heartburn cohort, TTO values (N = 40)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, (SD, range), y</td>
<td>65 (11, 42-89)</td>
<td>59 (12, 40-79)</td>
<td>.02</td>
</tr>
<tr>
<td>No. men/ total (%)</td>
<td>57/60 (95)</td>
<td>37/40 (93)</td>
<td>&gt; .05</td>
</tr>
<tr>
<td>No. mean years with reflux (SD, range)</td>
<td>17 (12, 0-60)</td>
<td>16 (12, 1-50)</td>
<td>&gt; .05</td>
</tr>
<tr>
<td>Veteran</td>
<td>55/60 (92%)</td>
<td>32/40 (80%)</td>
<td>&gt; .05</td>
</tr>
</tbody>
</table>

*Student t test; χ² test used for sex analysis. †Three of the patients in the current study did not have a history of heartburn symptoms but were found to have BE.

### TABLE 2. Health-state utility assessments

<table>
<thead>
<tr>
<th>Parameter*</th>
<th>Cancer risk cohort (N = 60)</th>
<th>Heartburn cohort (N = 40)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual analog scale</td>
<td>0.68 (0.19)</td>
<td>0.71 (0.19)</td>
<td>.23</td>
</tr>
<tr>
<td>Mean TTO score</td>
<td>0.91 (0.13)</td>
<td>0.91 (0.11)</td>
<td>.96</td>
</tr>
<tr>
<td>Mean score food and drink subscales QOLRAD</td>
<td>5.44 (1.6)</td>
<td>5.12 (1.8)</td>
<td>.37</td>
</tr>
</tbody>
</table>

*Values shown are mean (SD) while all patients are on PPI therapy. Ranges in parentheses are for each utility value. †Mean TTO scores, comparing values derived for nondysplastic BE and the symptom-derived values from the prior study.
the 19 patients with a diagnosis of BE established 1 year or less (mean value of 0.92) compared with the 41 patients who had received the diagnosis more than a year ago (mean value of 0.90, \( P = .3 \)). Eleven (18%) of the patients did not have a prior upper endoscopy; the mean TTO value in these patients was 0.92 compared with 0.91 in the patients who had received the diagnosis more than a year ago. 

When patients were faced with a scenario of BE with LGD (0.85 [0.12], \( P = .02 \)) compared with nondysplastic BE and BE with HGD (0.77 [0.14], \( P = .002 \)) compared with BE with LGD), when patients were instructed to imagine esophageal cancer, the mean TTO score was 0.67 (0.19) (\( P = .002 \)). The overall correlation between health-state utility values and GERD-specific survey scores was low (\( r = 0.34 \)). The scatterplot matrix in Figure 2 shows all pairwise plots of the logit-transformed values for visual analog scale and the health-state utility values, as well as scores on the symptom surveys. Scatterplots of the data demonstrated a good correlation (\( r > 0.7 \)) between the scores obtained by using the visual analog scale and the mean health-state utility values, but little to no correlation between the utility scores and the scores from the disease-specific surveys (\( r < 0.5 \)). There was poor correlation (\( r < 0.5 \)) between the TTO scores for nondysplastic and dysplastic states and the TTO value for esophageal cancer.

We used a previously published regression equation by Nichol et al\(^\text{45}\) in an attempt to estimate the health-state utility values from the SF-36 scores. Results are shown in Figure 3. The \( r \) values for the TTO values (\( r = 0.25 \)) and the transformed scores (\( r = 0.22 \)) were low, demonstrating the additional value to measuring the utility, which is a preference-weighted measure, whereas the SF-36 is not preference weighted.

Separate regression analyses were performed for the TTO scores by using the overall mean TTO score as the dependent variable, and age, veteran status, number of years on medications, years with heartburn symptoms, and presence of comorbid conditions as the independent variables.

For the TTO score for nondysplastic BE, the full-fitted model (mean values \( \pm \) SEM) was log \( p/(1 - p) = (2.5 \pm 0.22, P < .001) + (3.3 \pm 1.8 \times \text{years on medication/age, } P = .08) \). This model suggested that a higher score on the TTO exercise was possibly associated with the number of years on antisecretory therapy. Because the responses were transformed by using the started logit transformation, the coefficients of the model estimate log odds ratios.

For the TTO score for the LGD scenario, the full-fitted model was log \( p/(1 - p) = (1.8 \pm 0.24, P < .001) + (4.0 \pm 2.0 \times \text{years on medication/age, } P = .05) \). For the TTO for HGD, the model was the same with a \( P \) value for years of medication/age of approximately .04.
When a model was fitted for the cancer TTO value, the model was log \( p/(1 - p) = (0.9 \pm 0.4, P = .02) + (7.2 \pm 2.2 \times \text{years on medication/age}, P = .002) + (-2.2 \pm 0.93 \times \text{years with symptoms/age}, P = .02) \), which suggests that a higher score was associated with increased number of years on medications and younger age.

**DISCUSSION**

BE is a premalignant condition that affects approximately 5% to 20% of patients with chronic GERD. We previously demonstrated that the impact on health utility from GERD is significant. When patients are off reflux
medications, the symptom-derived TTO values for patients with heartburn and BE were not statistically different and approached the TTO values obtained for patients with other serious conditions, such as angina pectoris (0.93), New York Heart Association Class II congestive heart failure (0.90), coronary heart disease (0.85), chronic obstructive pulmonary disease (0.95), and asthma (0.89).

The purpose of this study was to define the impact on health-related quality of life associated with the underlying cancer risk associated with BE instead of the decrement from chronic heartburn symptoms. For patients with non-dysplastic BE, the TTO values were equivalent to the symptom-derived values while patients were on antisecretory therapy in our previously published study of 158 patients with GERD that included 40 patients with BE. However, the TTO values for hypothetical states of dysplasia (cancer risk of 2.5% or greater) were significantly lower. Our study illustrates the importance of accurate cancer-risk estimation and patient education about the cancer risk associated with BE.

In this study, we elected to use the TTO methodology to elicit utility values and not the standard gamble assessment. In the standard gamble, subjects are asked to engage in a gamble between the chance of a cure and the risk of death until they find a risk level where they are ambivalent between the 2 health states. In our prior study of patients with GERD and BE, we found that the values obtained by using the standard gamble assessment were higher than those obtained from the TTO technique. Prior studies that have also shown standard gamble uses exceeding the values obtained from TTO technique have advocated that TTO utilities might reflect patient preferences for health more accurately than standard gamble scores. The reason for this finding is that most individuals are risk averse and so they prefer to give up a stated amount of time, as in the TTO assessment, rather than to take a risk with uncertainty, as in standard gamble. We, therefore, did not elicit utilities with standard gamble in this study because of the findings from the literature and our prior analysis in GERD patients.

As in our prior quality-of-life study, there was little to no correlation between symptom scores on standardized GERD-specific surveys and the TTO scores, suggesting that disease-specific surveys may not accurately reflect patients’ assessment of global health-related quality of life. In addition, the GERD-specific surveys do not inquire about the presence of BE or the potential cancer risk. These results demonstrate the additional value from measurement of the utility, which is a preference-weighted measure, whereas the SF-36 is not preference weighted.

We found that the duration of antisecretory therapy was an important predictor of the TTO score and that younger patients would be more likely to have a higher TTO score for the cancer scenario. The likely reason for this result is that individuals tend to adjust to chronic illnesses over time, which might account for a higher score on a utility testing.

We obtained the cancer risk associated with LGD from the current literature. However, data from the Seattle Barrett’s Esophagus Registry have suggested that patients with nondysplastic BE and LGD likely have equivalent cancer risks. When flow cytometry was performed in patients with BE, 10% of patients with nondysplastic BE and LGD had abnormal profiles. In this cohort with positive-flow abnormalities, the progression to cancer was shown to be approximately 5% per year for both nondysplastic BE and LGD. Therefore, while it is likely that the

Figure 3. Estimation of health-state utility values by using transformed SF-36 scores. There is a poor correlation between the transformed SF-36 values and the health-state utility values.
cancer risk we used for the state of LGD was too high for most patients with LGD who will have normal flow cytometry profiles, our study showed that increasing cancer risk is associated with decreased health-related quality of life. The role of patient education on perceived cancer risk and subsequent health-related quality-of-life values has not yet been studied. In addition, we assessed the ability to understand the concept of TTO by using a practice question regarding a hypothetical scenario of vision loss. While all of the patients were able to understand the practice question, we did not formally assess their numeracy abilities. Again, patient education about hypothetical risks and impact on utility values would add insight into this issue.

Potential weaknesses of our study include the fact that we studied a relatively small number of patients with BE and that the patients who responded to the invitation to participate might have been most concerned about their risks of cancer, which could have resulted in lower TTO values. However, this seems unlikely, because the TTO values for nondysplastic BE were not significantly different from those obtained in the prior symptom-based study in 158 patients with GERD. Another potential weakness of our study is that we did not measure the TTO values for heartburn symptoms and cancer in the same patients so that patients could have served as their own controls. In addition, the cancer risks were presented in a sequential fashion of increasing risks of cancer, instead of a random sequence. It is possible that this sequential ordering might have altered our results, because most of the patients did not have dysplasia, and the theoretical values for dysplasia may be lower than in actual patients with the condition. A multicenter study would be needed to recruit adequate numbers of patients with dysplastic BE. Finally, the TTO values for cancer were also theoretical and need to be compared in future studies that obtain TTO values in patients who actually have esophageal cancer and have undergone esophagectomy.

In summary, we have demonstrated that the risk of esophageal cancer associated with BE can adversely affect patients’ health-related quality-of-life in addition to the symptoms of heartburn. The values defined in this analysis will be useful for future cost-effectiveness analyses to determine the most appropriate treatment for BE, particularly for patients with dysplasia and/or early cancer.

**DISCLOSURE**

None of the authors have any disclosures to declare regarding the submitted manuscript. The views expressed are those of the authors and not necessarily those of the Department of Veterans Affairs.

**REFERENCES**


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